Remarks

In view of the following remarks, reconsideration and withdrawal of the Examiner's rejections are requested respectfully.

Status of the Claims

The Examiner's Action consists of a rejection of all pending claims, namely Claims 1 to 5 and 20 to 35. Claim 1 has been amended. Claims 36-40 have been added. No claims have been cancelled. Accordingly, Claims 1 to 5 and 20 to 40 are presented for the Examiner's consideration.

Summary of the Examiner's Rejections

Claims 1 to 5, 21 to 22, 25 to 27, and 31 to 35 were rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,080,736 to Landry *et al.* (the Landry reference) in combination with U.S. Patent No. 6,066,339 to Stark *et al.* (the Stark reference).

Claims 1 to 5, 20 to 32, and 35 were rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 4,851,228 to Zentner *et al.* (the Zentner reference) in view of the Stark reference.

Summary of Applicants' Invention

Applicants' invention relates to a pharmaceutical formulation which can be used for the treatment of depression or obsessive compulsive disorder. According to

an aspect of the invention, the formulation for oral administration comprises: 1) particles of a selective serotonin reuptake inhibitor (SSRI) or a pharmaceutically acceptable salt thereof, which particles are 2) coated with a rate-controlling polymer which allows controlled release of an SSRI over a period of not less than about 12 hours following oral administration. Fluvoxamine is an example of an SSRI.

The SSRI particles of the formulation may take the form of pellets or beads which comprise a core. The core may also comprise an organic acid. The core is coated with a rate-controlling polymer which forms a rate-controlling membrane surrounding the core. The rate-controlling membrane is effective in providing a controlled release of an SSRI over a period of not less than about 12 hours following oral administration.

The discussion which follows demonstrates that the combined disclosures of the cited references do not render the present invention obvious. A summary of each reference and of the Examiner's rejections appears immediately below.

Summary of the References

The references cited by the Examiner in support of the § 103 rejections are summarized below.

U.S. Patent No. 6,080,736 to Landry et al.

The Landry reference relates to a method for treating anxiety or anxiety disorders by administering the R enantiomer of tofisopam (R-tofisopam, or a salt thereof, hereinafter referred to as the "active ingredient") substantially free of the S enantiomer. This reference discloses also that the active ingredient can be

administered along with or in conjunction with other psychiatric medications or psychoactive compounds, including, for example, fluvoxamine. See, column 13, lines 59-65 and column 16, lines 30 to 44 of the Landry reference.

Although the Landry reference discloses that the active ingredient can be formulated in a controlled-release form (column 16, lines 55-56, and column 17, lines 53-65), it does not disclose a controlled-release form of the "other psychiatric or psychoactive compounds." There is no disclosure whatsoever in the Landry reference of SSRI "particles . . . coated with a rate controlling polymer." Likewise, none of the Examples in the Landry reference exemplify SSRI "particles . . . coated with a rate controlling polymer."

U.S. Patent No. 6,066,339 to Stark et al.

The Stark reference relates to an oral morphine multiparticulate formulation for once-daily administration comprising sustained release particles. The core, referred to as applied beads or immediate release (IR) beads, is formed by building up a morphine active agent and osmotic agent on an inert core. See, column 5, lines 18-22 of the Stark reference. The sustained release particles are formed by coating the applied beads with a rate-controlling polymer comprised of ammonio methacrylate copolymers in an amount sufficient to achieve therapeutically effective plasma levels of morphine over at least 24 hours in the patient. See, column 2, lines 58-65 of the Stark reference. A portion or all of the sustained release particles further include an immediate release coating applied onto the rate-controlling polymer coat. The immediate release coating includes water soluble morphine and optionally an osmotic agent. See, column 3, lines 20-24 of the Stark reference.

There is no disclosure whatsoever in the Stark reference concerning SSRIs. Furthermore, the Stark reference does not disclose applicants' claimed release profile

for morphine particles, as acknowledged by the Examiner on page 4 of the Office Action. The Stark reference has been cited, on page 6 of the Final Office Action, solely for the teaching of rate-controlled coating.

U.S. Patent No. 4,581,228 to Zentner et al.

The Zentner reference relates to a multiparticulate osmotic composition (referred to in the patent as a "pump") for the osmotically controlled release of a pharmaceutically active agent to an environment of use. The composition comprises a carrier medium and a core composition mass (referred to also as a "core mass" in the specification) of at least one soluble pharmacologically active agent, a rate controlling, water-insoluble wall, a polymer permeable to water, but impermeable to solute, and at least one pH insensitive pore-forming additive dispersed throughout the wall. The Zentner reference also describes the core composition mass as being in the form of a solid conventional tablet, pellet, or multiparticulate. The core composition mass is encased by a controlled porosity wall. See, column 10, lines 59 to 62 of the Zentner reference. As disclosed in the Zentner reference, the wall is composed of a polymeric material that is insoluble in fluids of the environment of intended use and has a sponge-like structure composed of numerous open and closed cells through which the active agent is released after removal of the pore former. See, column 3, lines 29-47, and column 5, lines 44-51. The wall has programmable fluid transmission and agent release rates which provide for controlled release of agent which is free from environmental influences including pH and degree of external fluid agitation. See, column 1, lines 60-64 of the Zentner reference. Solubilized constituents incorporated into a core composition mass create a water activity gradient across the wall, resulting in osmotically actuated fluid movement constituting the osmotic pump action of the Zentner reference. See, column 11, lines 47-51. The Examples disclose continuous and uniform zero-order release of various beneficial drugs and Example 14 discloses a multiparticulate osmotic system.

The Zentner reference is silent with regard to the specific rate-controlled coating recited in Claims 5 and 32, as admitted by the Examiner. Although the Zentner reference at columns 12 to 14 lists fluvoxamine in a lengthy list of drugs for possible use in the osmotic pump, there are no examples disclosing SSRI "particles . . . coated with a rate-controlling polymer which allows controlled release . . . over a period of not less than about 12 hours following oral administration", as recited in Claim 1 and the claims that depend therefrom. Additionally, the Zentner reference discloses that the controlled release of the agent does not depend upon influences including pH and external fluid agitation, but is dependent upon the osmotic gradient between the core and fluid in the surrounding environment, which is distinguishable from the "rate-controlling polymer which allows controlled release" as recited in Claim 1, and the claims that depend therefrom.

Discussion of the Examiner's Rejections

Applicants acknowledge that the Examiner has withdrawn the rejections made in the first Office Action under 35 U.S.C. § 112. A discussion of the Section 103 rejections which the Examiner has maintained follows.

The § 103 Rejection Based on the Landry and Stark References

The claims distinguish over the disclosure of the primary reference in reciting a multiparticulate controlled release SSRI formulation which comprises: 1) particles of a SSRI or a pharmaceutically acceptable salt thereof, which particles are 2) coated with a rate controlling polymer which allows controlled release of the SSRI over a period of not less than about 12 hours following oral administration.

As mentioned above, the primary reference discloses that the active ingredient which is described therein can be formulated in a controlled-release form, but it fails

to disclose fluvoxamine (an SSRI) in particulate form or a controlled release formulation of the fluvoxamine. A general disclosure concerning other psychiatric compounds, such as fluvoxamine, is provided by the primary reference, but the particular form of such compounds is not disclosed. In each embodiment of the primary reference, the active ingredient is administered in a dosage form separate from the "other" psychiatric compounds disclosed. None of the examples discloses the active ingredient combined with the "other" psychiatric compounds, including fluvoxamine. Accordingly, the primary reference contains no disclosure of a controlled-release composition which comprises the "other" psychiatric compounds and it is clearly wrong for the Examiner to attribute such disclosure to the primary reference.

Assuming *arguendo* that a person skilled in the art went beyond the disclosure of the primary reference and decided to formulate a controlled-release composition which included both the "active" and "other" ingredient, the disclosure of the primary reference, as regards applicants' claims, is further deficient in that it does not disclose fluvoxamine in particulate form or the controlled release parameter recited in applicant's claims. The only disclosure of fluvoxamine in particulate form in a controlled release formulation appears in applicants' specification, not in the disclosure of the primary reference.

The secondary reference does not disclose fluvoxamine or any other SSRI and it discloses a release profile that is different from that recited in the claims. Accordingly, the combined disclosures of the primary and secondary references do not result in applicants' claimed subject matter.

The Examiner has asserted that a *prima facie* case of obviousness has been made. As set forth in the MPEP, Section 2143,

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the publications themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or publications when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

Contrary to the Examiner's assertion, a *prima facie* case of obviousness has not been made for the reasons which follow.

The Landry primary reference, when considered as a whole, is primarily directed to administration of R-tofisopam and presents one skilled in the art at the time of the invention with only generalized statements concerning the controlled release of the active ingredient, i.e., R-tofisopam. In view of the scant disclosure with regard to controlled release and lack of disclosure with regard to a rate-controlling polymer coating, one skilled in the art at the time of the invention would not glean information from the Landry reference to arrive at SSRI "particles . . . coated with a rate controlling polymer which allows controlled release" as recited in Claim 1 and the claims that depend therefrom. The Examiner has acknowledged also the lack of disclosure in the Landry reference with regard to rate controlling polymers.

As a secondary matter, the Landry primary reference discloses that R-tofisopam may possibly be administered "along with" or "in conjunction with other psychiatric or psychoactive compounds", which compounds include fluvoxamine. The Examiner has cited also Claims 1, 2, 12 and 15 of the Landry primary reference as indicating

that the dosage form further comprises an antidepressant, such as fluvoxamine. See, pages 5 to 6 of the Final Office Action.

Aforementioned Claims 1, 2, 12 and 15 of the Landry primary reference define a method which includes treating a human with an antidepressant or 1,4-benzodiazepine. The cited claims do not recite expressly and, therefore, do not teach or suggest to one skilled in the art at the time of the invention: that R-tofisopam and fluvoxamine (or other antidepressant) are combined together into a dosage form. The Examiner's allegation that the pending claims are obvious based on the claims of the Landry primary reference is flawed because the function of the claims is to define the scope of protection sought, not to describe the invention. See, *In re Benno*, 768 F.2d 1340, 226 U.S.P.Q. 683 (Fed. Cir. 1985). It is a fundamental principle of patent law that the claims are construed in view of the descriptive portion of the patent. The phrases in the descriptive portion of the primary reference describing that R-tofisopam is administered "along with" or "in conjunction with" the "other compounds", coupled with the lack of a description of a composition which contains both ingredients, is a clear teaching to one skilled in the art that the primary reference teaches separate administration of the involved ingredients.

The Stark secondary reference fails to cure the deficiencies of the Landry primary reference, since there is no teaching or suggestion to modify the Landry primary reference to provide fluvoxamine in particulate form or to coat fluvoxamine particles with the "rate-controlling polymer" of the Stark secondary reference and arrive at the invention as claimed.

Neither the Landry primary reference nor the Stark secondary reference provides motivation to substitute an SSRI in particle form using the alleged slow/controlled release formulation of the Stark secondary reference for arriving at a

result of "controlled release of said SSRI over a period of not less than about 12 hours" as recited in Claim 1 and the claims that depend therefrom. One skilled in the art would not be motivated to substitute an SSRI in particulate form, since the Landry primary reference does not disclose any particular form of fluvoxamine and the Stark secondary reference does not disclose SSRIs or fluvoxamine.

Therefore, in view of the foregoing, one with skill in the art at the time of the invention, after reading the entire Landry and Stark references, would not be led to "modify Landry's multi-layer coating formulation" as suggested by the Examiner on page 3 of the Final Office Action, by "using the rate-controlling coating in view of the teaching of Stark" and arrive at the claimed invention which provides "controlled release. . .over a period of not less than about 12 hours." If one skilled in the art at the time of the invention had the foresight to combine the fluvoxamine of the Landry reference with the rate-controlling polymers of the Stark secondary reference, the result would still not reach the invention as claimed.

Since neither the Landry nor the Stark reference teaches, suggests, or provides motivation to use an SSRI, in particle form, for a controlled-release formulation which allows controlled release of the SSRI over a period of not less than about 12 hours following oral administration, a *prima facie* case has not been made. Accordingly, reconsideration and withdrawal of the rejection are requested respectfully.

The § 103 Rejection based on the Zentner and Stark References

As discussed above, Claim 1 distinguishes over the disclosure of the primary Zentner primary reference in reciting a multiparticulate controlled release SSRI formulation which comprises 1) particles of a SSRI or a pharmaceutically acceptable salt thereof, which particles are 2) coated with a rate-controlling polymer coating

which allows controlled release of the SSRI over a period of not less than about 12 hours.

The Zentner primary reference describes a composition which is referred to as a "multiparticulate osmotic pump" that includes a rate-controlling water-insoluble wall, a polymer permeable to water, but impermeable to solute, and a pH insensitive pore forming additive, also referred to as a "pore former." As water enters through the channels formed in the wall after removal of the pore former, the active agent is released through the channels at a controlled and continuous rate in response to fluid volume flux, resulting from the osmotic pressure gradient, and in response to diffusive flux, driven by the chemical potential gradient of the agent across the wall. Thus, the channels formed in the water insoluble wall of controlled porosity serve as the water entry and core composition solution exit sites.

Fluvoxamine is generally disclosed in a lengthy list of drugs (over two columns of the patent) for possible use in the pump of the Zentner primary reference. None of the examples discloses the use of fluvoxamine or any other SSRI.

The only example in which particles of the active agent are used is Example 14; the particles are compressed into a core mass and coated with the wall forming solution that includes sorbitol as the pore forming additive. With regard to fluvoxamine, the Examiner has alleged, on page 6 of the Final Office Action, that the recitation of fluvoxamine in the list of drugs in the Zentner primary reference "anticipates" Claim 1, and the claims that depend therefrom. If the Examiner maintains the rejection, clarification is requested respectfully as to whether the claims are rejected under 35 U.S.C. §§ 102 or 103.

Assuming *arguendo* that the Zentner primary references discloses fluvoxamine in particulate form, the Zentner primary reference fails to disclose fluvoxamine "particles. . .coated with a rate-controlling polymer which provides a controlled release over not less than about 12 hours after oral administration" as recited in Claim 1, and the claims that depend therefrom. The Examiner has asserted, and applicants agree, that the Zentner primary reference is silent with regard to the teaching of the specific rate-controlled coating recited in Claims 5 and 32. The Zenter primary reference also does not teach the claimed release profile.

The Zentner primary reference describes that the release of the agent through the water-impermeable wall is dependent upon the osmotic gradient between the contents of the core and fluid in the surrounding environment and refers to osmotically controlled release in the Examples at column 16, lines 33-34; column 19, lines 12-13 and 49-50; column 20, lines 17-18 and 67-68; column 21, lines 37-38; and column 22, lines 9-10. The Examples describe the release of potassium chloride, sodium indomethacin trihydrate, and cyclobenzaprine, yet there are no examples exemplifying osmotically driven drug delivery for controlled release of fluvoxamine or an SSRI. Hence, although "controlled release" is mentioned in the Zentner primary reference, release is dependent upon the osmotic gradient between the core and the fluid in the surrounding environment and the controlled porosity wall, in contrast to the "rate controlling polymer which allows controlled release . . . over a period of not less than about 12 hours" as recited in Claim 1, and the claims that depend therefrom.

The addition of the Stark secondary reference fails to cure the deficiencies of the Zentner primary reference because there is no teaching, suggestion, or motivation provided by the references to modify the Zentner primary reference by coating SSRI particles with a rate-controlling polymer which allows controlled release in order to arrive at the controlled release formulation of the invention as claimed. Furthermore,

since the Zentner primary reference fails to exemplify the release of an SSRI in particulate form from a rate-controlling polymer coating, the addition of the alleged "similar" release profiles from the Stark secondary reference, mentioned by the Examiner on page 4 of the Final Office Action, is insufficient to render the claimed invention obvious.

With regard to Claims 5 and 23, the Examiner's proposal to substitute the ammonio methacrylate copolymers of the Stark reference in the Zentner formulation would result in a basic modification of the Zentner et al. "water-insoluble wall" that is entirely inconsistent with the characterization of the primary reference which discloses that the wall has a sponge-like structure composition open and closed cells through which the active agent is released after the removal of the pore former element of the wall. However, the copolymer constituent of the Stark reference has no pore former and, accordingly, substituting the copolymer of the Stark reference for the wall-forming element of the primary reference and results in a structure not contemplated or wanted by the Zentner et al. inventors.

It also would not have been obvious for one of ordinary skill in the art at the time of the invention to "by routine experimentation determine a suitable release rate useful to deliver SSRI compound" as alleged by the Examiner, and arrive at the invention as claimed. The need for experimentation to determine parameters needed to make a device work is an application of the often rejected "obvious to try" standard and falls short of statutory "obviousness" of 35 U.S.C. § 103. See, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 5 U.S.P.Q. 2d 1434 (Fed. Cir. 1988). Thus, the Examiner's emphasis upon routine experimentation is contrary to the statutory requirements of 35 U.S.C. § 103.

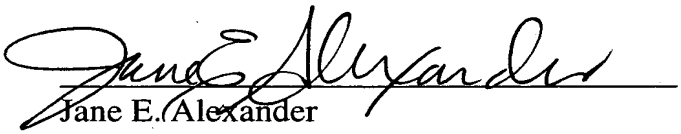
Accordingly, reconsideration and withdrawal of the rejection are requested respectfully.

The amendment to Claim 1 places the rejected claims in better form for consideration on appeal, for which entry is permitted under 37 C.F.R. 1.116. New claims 36-40 have been added, but do not require an additional search by the Examiner. Therefore, it is requested respectfully that the claim amendments be entered for purposes of appeal in the event the claims are not deemed by the Examiner to be in condition for allowance. It is believed, however, that all rejections of the Examiner have been addressed, and that the claims are in condition for allowance for the foregoing reasons. In the event that any outstanding issues remain, the Examiner is invited to telephone the undersigned.

A check to cover the extra claim fee is enclosed. If there is any error in the fee submitted, please charge or credit the difference to Deposit Account No. 19-5425. A duplicate of this Reply is attached.

This Reply is accompanied by "Version with Markings to Show Changes Made" respecting the amendments to the claims.

Respectfully submitted,
Synnestvedt & Lechner LLP



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 1. (Amended) A multiparticulate controlled release selective serotonin reuptake inhibitor (SSRI) formulation for oral administration, which comprises particles of said SSRI or a pharmaceutically acceptable salt thereof coated with a rate controlling polymer which allows controlled release of said SSRI over a period of not less than about 12 hours following oral administration.